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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/994,909	11/23/2001	George Jackowski	2132.090	7376

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,909	JACKOWSKI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 November 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. The traversal is on the ground(s) that SEQ ID NOS: 1-4 are fragments of the same complement C3 precursor protein, they are identified as markers predictive of Alzheimer's disease, thus, they share a common utility and common structural feature and, therefore, claims 1, 18, 29, 30, 33, 34 and 38 are proper Markush claims. These arguments have been found to be persuasive in part. The Examiner acknowledges that because polypeptides of SEQ ID NO: 1-4 are asserted to be indicative of Alzheimer's disease and, therefore, share a common utility, the objections to the claims 1, 18, 29, 30, 33, 34 and 38 as being improper Markush claims is withdrawn. However, because each of the recited sequences represents a non-overlapping fragment of a larger sequence and each fragment could be embedded within other patentably distinct proteins, a separate search is required for each possible fragment, the restriction is still deemed proper. Applicant's argument regarding examination of "four short amino acid sequences, six sequences less than the ten sequences normally considered by the Office as reasonable for examination purposes" (bottom at page 3 of the Response) has been fully considered but is not deemed to be persuasive for the following reasons. MPEP 804.03 is directed to nucleotide sequences, in which the Commissioner authorized a partial waiver of restriction practice, allowing the examination of up to ten sequences. This waiver was issued in 1996. Since then, the nucleic acid and protein databases that must be searched for each of the independent and distinct sequences claimed herein have multiplied many fold in size, such that it is now burdensome to search more than a single sequence in an application. Further, the waiver allowed, but did not require the Examiner

to search up to ten sequences. Also, the waiver was directed to nucleotide sequences and not amino acids sequences, which is the case in the instant application.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 1 and 2, in so far as they are directed to SEQ ID NO: 1 are under examination in the instant office action.

Sequence compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence listing has been provided which includes the amino acid sequences presented in Figure 2 of the instant specification. In case these sequences are new, Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d)

which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1 and 2 are drawn to a biopolymer marker of SEQ ID NO: 1 or at least one analyte thereof. First, it is clear for the instant specification, that SEQ ID NO: 1 is a fragment of a larger molecule cleaved by proteolytic enzymes during processing of a sample according to the protocol on pages 40-46. However, it is contemplated on pages 38-39 of the instant specification, that the fragmentation pattern of such larger molecules is specific and unique for certain disease conditions. Thus, it appears that a peptide of SEQ ID NO: 1 could be a naturally occurring peptide. Moreover, according to the definition, an "analyte" is "any atom and/or molecule; including their complexes and fragment ions. The term may refer to a single component or a set of components"(see page 6, lines 15-17 of the instant specification). Therefore, "an analyte" of claims 1 and 2 clearly encompasses naturally occurring atoms and molecules.

Thus, claims 1 and 2 fail to include any limitations, which would distinguish the claimed polypeptide sequences from those which occur in nature. In the absence of the hand of man, naturally occurring nucleic acid molecules and proteins are considered non-statutory subject

matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, mere purity of a naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui, 156 USPQ 426 (1966). However, when purity results in a new utility, patentability is considered. Merck Co. v. Chase Chemical Co., 273 F. Supp. 68 (1967). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment of the claims to recite a purity limitation, if supported by the specification, is suggested to obviate this rejection. Applicant should point to the basis in the specification for any amendment to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claim 1 is drawn to a biopolymer marker of SEQ ID NO: 1 useful in indicating at least one particular disease state. Claims 2 encompasses the biopolymer marker of SEQ ID NO: 1 as being predictive of Alzheimer's disease. However, the instant specification fails to provide any guidance on how to use the disclosed polypeptide of SEQ ID NO: 1 as a marker or indicator of any disease state, including Alzheimer's disease. There is no information disclosed in the instant specification, which would provide evidence or sound scientific reasoning that a biopolymer marker, which is a polypeptide of SEQ ID NO: 1, is specifically associated with any particular

disease state in general or with Alzheimer's disease in particular, thereby requiring undue experimentation by a skilled artisan to discover how to make and use Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention is the finding of specific fragments of complement C3 precursor protein, which are polypeptides of SEQ ID NO: 1-4 and which are asserted to be associated with Alzheimer's disease, in a serum sample treated according to a protocol provided on pages 40-46 of the instant specification. The state of the art is such that it does not recognize any specific association of the polypeptide of SEQ ID NO: 1 with any particular disease state or with Alzheimer's disease. Therefore, in the absence of information in the prior art, one skilled in the art would have to solely depend on the instant disclosure to practice the claimed invention. Accordingly, the instant invention, as claimed, allows the detection of a peptide of SEQ ID NO: 1 in general to lead to diagnosis of a disease state. However, the instant specification provides no information on how the detection of a biopolymer marker of SEQ ID NO: 1 in any sample in general can be useful in detecting any particular disease state, including Alzheimer's disease.

Furthermore, it is stated on page 46, last paragraph and page 47, first paragraph, that "Figures 1 and 4 are photographs of a gel which is indicative of the presence/absence of the

marker in disease vs. control and, in cases where the marker is always present, the relative strength, e.g. the up or down regulation of the marker relative to categorization of disease state is deduced". Based on the limited information on how to conduct mass spectrometric analysis of a sample presented in the instant specification and on the analysis of Figures 1 and 4, one skilled in the art clearly would not be able to use the polypeptide of SEQ ID NO: 1 as a biopolymer marker for a particular disease state or for Alzheimer's disease. First, the instant specification fails to explain the relationship between a polypeptide of SEQ ID NO: 1 and "particular disease state". While it is not necessary that Applicant understands or discloses the mechanism by which the invention functions, in this case, in the absence of such an understanding the following questions must be answered. Is it "the up or down regulation of the marker relative to categorization of disease state"? Or is "the presence/absence" of the polypeptide of SEQ ID NO: 1 indicative of a disease? Because this critical information is not provided in the instant specification, as filed, undue experimentation is required to answer these questions.

Also, it is well known in the art that a diagnosis of Alzheimer's disease is only definitive at postmortem examination or at brain biopsy (see Clark et al., 1993, and Motter et al, 1995, for example). The instant specification, as originally filed, fails to disclose any specific information regarding the data presented in Figures 1 and 4, such as, for example, description of a sample, the representative number of samples, description of control samples, and, most importantly, a method of evaluation of the bands displayed on Figures 1 and 4, which lead to a conclusion that they are indicative of Alzheimer's disease. The text on page 11, third paragraph, states that "a biopolymer marker which is strongly present in a normal individual, but is down-regulated in disease is predictive of said disease; while alternatively, a biopolymer marker which is strongly

present in a disease state, but is down-regulated in normal individuals, is indicative of said disease state". Based on this information, a skilled artisan would have to resort to substantial amount of undue experimentation to discover how to use the claimed biopolymer marker of SEQ ID NO: 1 in prediction of Alzheimer's disease.

Thus, Applicant's invention is predicated on the finding that a serum sample being processed according to the disclosed protocol contains SEQ ID NO: 1. Applicant further extrapolates this result into an assertion that SEQ ID NO: 1 is useful as a biopolymer marker for Alzheimer's disease or for any disease state in general. Accordingly, it would appear that Applicant provides a single finding (the finding), and then presents an invitation to experiment to determine if a polypeptide of SEQ ID NO: 1 is useful in indicating at least one particular disease state. Such experimentation would include determination if a marker of SEQ ID NO: 1 is absent or present or strongly present in a normal individual, or is up- or down-regulated in disease.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one

skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not follow the guidance presented therein and use the claimed biopolymer marker without first making a substantial inventive contribution to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 is vague and indefinite because it is not clear whether "analyte thereof" refers to a biopolymer marker or to SEQ ID NO: 1. According to the instant specification, "biopolymers" are defined as "biological molecules/macromolecules" and an "analyte" is defined as "any atom and/or molecule; including their complexes and fragment ions" (page 6, lines 15-19). Thus, the definitions of these two terms appear to be conflicting, because one would not recognize an atom as a biopolymer. Clarification is required.

7. Claim 2 is indefinite for being dependent from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Walsh, 1977, Enzymatic Reaction mechanisms, W.H. Freeman and Company, p. 425-426.

Claim 1 is directed to a biopolymer marker of SEQ ID NO: 1 or at least one analyte thereof useful in indicating at least one particular disease state. An "analyte", according to the instant specification, is defined as "any atom and/or molecule; including their complexes and fragment ions. The term may refer to a single component or a set of components" (page 6, lines 15-17). Thus, claim 1 encompasses a molecular embodiment, the structural feature of which can be an atom, or a molecule, such as an amino acid.

Although claim 1 is not limited to a biopolymer marker consisting of one amino acid, during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). For art purposes interpretation, the preamble of the claim, which is the intended use of the "analyte" as a biopolymer marker for a disease state, is not given weight, see M.P.E.P. 2111.02, which states that during examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, e.g., In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963) (The claims were directed to a core member for hair curlers and a process of making a core member for hair curlers. Court held that the intended use of hair curling was of no

significance to the structure and process of making.); In re Sinex, 309 F.2d 488, 492, 135 USPQ 302, 305 (CCPA 1962) (statement of intended use in an apparatus claim did not distinguish over the prior art apparatus). If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim. See, e.g., In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997) (anticipation rejection affirmed based on Board's factual finding that the reference dispenser (a spout disclosed as useful for purposes such as dispensing oil from an oil can) would be capable of dispensing popcorn in the manner set forth in appellant's claim 1 (a dispensing top for dispensing popcorn in a specified manner)) and cases cited therein. See also MPEP § 2112 - § 2112.02.

Therefore, one would reasonably believe that claim 1 encompasses one amino acid, such as phenylalanine (Phe), which is present within SEQ ID NO: 1, as an analyte of a biopolymer marker useful in indicating one particular disease. Walsh describes a well-known pathological condition, phenylketonuria, which is characterized by elevated blood and urinary levels of phenylalanine. Therefore, disclosure of Walsh meets the limitations of claim 1.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
July 23, 2003